Case Docket No. **20693 US2**

NK-1 RECEPTOR ACTIVE AMINE OXIDE PRODRUGS

Continuity Information

[0001] This application is a divisional of U.S. Patent Application Serial No. 10/337,543, filed January 7, 2003, which is a divisional of U.S. Patent Application Serial No. 09/904,059, filed July 12, 2001, now U. S. Patent No. 6,593,472.

Field of Invention

[0002] The present invention is generally related to amine oxide compounds and more particularly to amine oxide compounds and pharmaceutically acceptable salts that are antagonists of the of the Neurokinin 1 (NK-1, substance P) receptor which are prodrugs for delivery of known compounds with antagonistic activity to the Neurokinin 1 (NK-1, substance P) receptor.

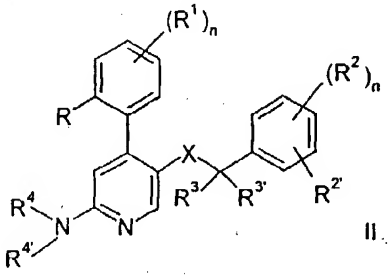
Background

[0003] A prodrug is in most cases a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. It has been shown that a molecule with optimal structural configuration and physicochemical properties for eliciting the desired therapeutic response at its target site does not necessarily possess the best molecular form and properties for its delivery to its point of ultimate action. Usually, only a minor fraction of doses administered reach the target area and since most agents interact with non-target sites as well, an inefficient delivery may result in undesirable side effects. This fact of differences in transport and in situ effect characteristics for many drug

molecules is the basic reason why bioreversible chemical derivatization of drugs, i.e., prodrug formation is a means by which a substantial improvement in the overall efficacy of drugs can often be achieved. Prodrugs are designed to overcome pharmaceutically and/or pharmacokinetically based problems associated with the parent drug molecule that would otherwise limit the clinical usefulness of the drug.

[0004] In recent years several types of bioreversible derivatives have been exploited for utilization in designing prodrugs. Using esters as a prodrug type for drugs containing carboxyl or hydroxyl function is most popular. Further well-known are prodrug derivatives of peptides, 4-imidazolidinones and the like, described in *Drugs of the Future, 1991, 16(5), 443-458* or N-oxides, described for example in US 5.691.336.

[0005] The compounds of formula II



II

are antagonists of the neurokinin receptor. The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645).

[0006] "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, 1993 reviews the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by

thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyper-reactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases.

[0007] Furthermore, Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

[0008] The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting.

[0009] In addition, in The New England Journal of Medicine, Vol. 340, No. 3 190-195, 1999 describes the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.

[0010] Further, the usefulness of neurokinin 1 receptor antagonists for the treatment of certain forms of urinary incontinence is described in Neuropeptides, 32(1), 1-49, (1998) and Eur. J. Pharmacol., 383(3), 297-303, (1999).

[0011] Furthermore, US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1 receptor antagonist.

Summary

[0012] The present invention relates to N-oxides of compounds of the formula